Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

High-sensitive cardiac troponin T as a marker of hemorrhagic complications in elderly patients anticoagulated for non-massive pulmonary embolism.

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Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

Abstract

Background: Recent data have raised concerns about the risk/benefit ratio of thrombolysis in non-high risk pulmonary embolism patients due to increased serious bleeding events. Whether cardiac biomarkers could be of help for bleeding risk stratification in this setting remains elusive.

Objectives: To determine the prognostic accuracy of hs-cTnT, NT-proBNP, RIETE and PESI score for the occurrence of clinically relevant bleeding (CRB) in elderly patients under conventional anticoagulation therapy for non-massive pulmonary embolism (NMPE).

Methods: We evaluated 230 elderly patients with available blood sample taken within one day from diagnosis. The primary study endpoint was CRB at 1, 3 and 24 months. Prognostic accuracies and associations were determined using C-statistics and subhazard ratios (SHR), respectively.

Results: hs-cTnT displayed the highest discriminatory power at 1 month (C-statistics: 0.77, 95% CI: 0.68–0.88) which remained stable over time. Although C-statistics comparison indicated that hs-cTnT was not statistically superior to RIETE score (0.77 vs 0.67, p=0.11), adding hs-cTnT to RIETE score significantly improved the C-statistics from 0.67 to 0.78 (p=0.02). SHRs indicated that for each hs-cTnT log-unit increase, there was a 58% increase in the risk of CRB independently of the RIETE score (adjusted SHR: 1.58, 95% CI: 1.31-1.92). At the pre-specified cut-off of 14 ng/l, the negative predictive value of hs-cTnT was 96.9% (95% CI: 91.4-99.0) and 94.9 (95%CI: 88.6-97.8) at 1 and 3 months, respectively.

Conclusion: In elderly, hs-cTnT provides incremental prognostic information over the RIETE score and could represent a valuable tool to identify NMPE patients at low risk of bleeding.

Keywords: Natriuretic Peptide, Brain ; Troponin T ; Pulmonary Embolism ; Hemorrhage ; RIETE score

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Abbreviations list

CRB : clinically relevant bleeding

NMPE : non-massive pulmonary embolism

PE : pulmonary embolism

SHR : subhazard ratios

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Introduction

Risk stratification in hemodynamically stable patients with pulmonary embolism (PE) has gained considerable interest as being susceptible to discriminate between non-massive PE patients at low-risk or those at intermediate risk of complications, which could respectively be either eligible for an outpatient treatment or susceptible to benefit from thrombolysis on top of conventional anticoagulation therapy (1–4). Currently, the identification of low-risk patients mostly rely on the pulmonary embolism severity index (PESI) score known to be effective in safely identifying such patients that could possibly be treated in an ambulatory fashion (1,4,5). Cardiac biomarkers, such as B-type natriuretic peptides (BNP and NT-proBNP) and cardiac troponin have also shown an interesting potential for rule-out purposes given their negative predictive values above 95% in predicting PE-related complications (6–12), and their ability to provide incremental prognostic information to PESI score in elderly patients (11). On the other hand, the optimal identification and management of intermediate risk patient is still unclear. Knowing whether radiological or biochemical features of right ventricular dysfunction/dilatation should be used for such purpose is still elusive. Furthermore, current evidences provided by the Pulmonary Embolism Thrombolysis (PEITHO) randomized-controlled study do not support the need of a more aggressive management by fibrinolysis to improve short or long term outcomes of such patients (13,14). If those results can be interpreted as the absence of thrombolysis benefit in PE patients at intermediate risk, they may also emphasize the need of a prompt and accurate major bleeding risk assessment before fibrinolytic therapy administration.

Because several cardiac biomarkers-oriented clinical trials in PE used composite endpoints including the occurrence of bleeding complications (6,7,9–11), and because natriuretic peptides and troponins have been respectively shown to act *in vitro* and *in vivo* as anticoagulant (15–17) and anti-angiogenic factors (18–21), we hypothesized that high-

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sensitive cardiac troponin T (hs-cTnT) and NT-proBNP levels upon admission could also reflect the global endothelial integrity of the vascular bed, and thereby could predict the patient propensity of bleeding while under anticoagulation therapy. Therefore, we challenged the prognostic accuracies of hs-cTnT and NT-proBNP, alone and in combination, to predict hemorrhagic complications prediction, and compared them to the RIETE score which is dedicated to assess the hemorrhagic risk in PE patients under anticoagulation (22,23).

Methods

Patient population and study design

The present study is an ancillary study of a swiss prospective cohort study (SWITCO65+) which involved university as well as high-volume non-university hospitals. SWITCO65+ aimed at assessing long-term outcomes of patients aged 65 or older with a diagnosis of deep vein thrombosis (DVT) or PE (5,11,12). The study protocol was approved by the research ethics committee of each institution, and all patients provided written informed consent.

A total of 695 patients with acute PE diagnosed from September 2009 to March 2012 were considered for this study. PE diagnosis was retained after documentation of a DVT with compression ultrasonography or angiography or when diagnostic imaging were either positive for PE (pulmonary angiography or spiral CT) or indicated PE with a high probability (ventilation perfusion scintigraphy) (5,11,12). Briefly, exclusion criteria included thrombosis at a site other than lower extremity or thrombosis related to catheter insertion, inadequate fluency in German or French, conditions making follow-up unlikely (i.e. terminal illness) or informed consent unavailable (i.e. severe dementia) and previous enrolment in the cohort.

For the present study, 10 patients with massive PE as defined with a systolic blood pressure ≤ 90 mmHg (1), as well as 8 patients not allowing use of their personal data or withdrawing

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consent within one day from inclusion, and 450 patients for which blood samples were obtained later than one day after diagnosis were excluded. In total, 230 patients were available for the analysis. Baseline demographic characteristics, clinical data and clinical scores (PESI (24) and RIETE scores) were prospectively collected by medical records review performed by trained research nurses.

Patients' follow-up

Follow-up was obtained for all patients at 1, 3 and 24 months months after enrolment. Patients as well as physicians in charge were told to refer to the investigators whenever recurrent respiratory or lower extremity symptoms occurred. Telephone interviews and face-to-face evaluations of all patients were organized at the end of the follow-up period by study coordinators who remained blinded to the results of analyses (25). All health-related events were reported by patients after hospital discharge (readmission to the hospital, any medical appointment, treatment modification, medical investigation and/or hemorrhagic complication). Review of medical files and contact with the family doctor were performed in case of suspected clinical event.

Definition of endpoints

The predetermined primary endpoint of this study consisted in clinically relevant bleedings (i.e. combination of clinically relevant non-major bleeding as well as major bleeding).

Clinically relevant nonmajor bleeding episode was defined as bleeding not meeting the definition of major bleeding, but requiring physician consultation or evaluation in the emergency department (26).

The secondary endpoint consisted in major bleeding defined as: i) fatal bleeding, and/or ii) symptomatic bleeding at a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome), and/or iii) overt

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bleeding with a reduction in haemoglobin levels of ≥20 g/L or leading to transfusion of at least two units of packed red blood cells (27).

Primary and secondary endpoints were adjudicated upon the consensus of a committee that was blinded to biochemical results.

Sample Collection

Blood collection and sample processing details were described elsewhere (28).

Biochemical Analyses

Blood samples were analysed to the University Hospitals of Geneva so as to minimize analytical bias. NT-proBNP and hs-cTnT were measured by electrochemiluminescence methods on routine autoanalysers (Elecsys™, Roche, Switzerland). We used a cut-off of 14 ng/l for hs-cTnT and 300 pg/ml for NT-proBNP. Details for justification of these cut-offs were described elsewhere (7,11,12,28,29).

RIETE score assessment

The RIETE score allows the determination of major bleeding risk in patients undergoing anticoagulation treatment for pulmonary embolism (22,23). This score is computed for each patient according to the presence of six clinical features, including anamnesis of recent bleeding (< 2 weeks), creatinine value above 106 µmol/L, presence of anemia (Hb <12 g/dL for women, Hb <13 g/dL for men), presence of malignancy, clinically overt PE, and age >75 years old (22,23). As shown in Table 1, each of these items has a specific weighting which is summed together to generate a total score with the following risk classes: 0 = low risk, 1-4 = intermediate risk, above 4 = high risk (22,23).

Table 1. RIETE bleeding risk score and risk classes

Items	*Points*
Recent major bleeding	2
Creatinine levels >109 µmol/l	1.5

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Anemia	1.5
Cancer	1
Clinically overt PE	1
Age >75 years	1

Incident risk of major bleeding per risk class	***Corresponding cumulated points***
Low risk: 0.3% (95% CI: 0.1-0.6%)	0
Intermediate Risk: 2.6% (95% CI: 2.3-2.6%)	1-4
High risk: 7.3% (95% CI: 5.6-9.3%)	> 4

Adapted from (22,23)

Statistical analysis

A Chi-squared test or a non-parametric Wilcoxon rank-sum test were used as appropriate to compare patients baseline characteristics with and without clinically relevant bleeding. The Kaplan-Meier technique and the log-rank test were used to estimate and compare the cumulative incidence of outcomes for categories of biomarker levels. For hs-cTNT and NT-proBNP, we used the prospectively defined and validated cut–offs of 14 ng/l and 300 pg/ml, respectively (11,12). The discriminative ability of the biomarker levels and the clinical scores for events up to 1, 3 and 24 months was assessed by Harrell's C concordance statistics, which is equivalent to the area under the ROC curve (AUC) in the case of binary outcomes. Associations of biomarker levels and clinical scores with outcomes were assessed using competing-risk regression accounting for non-bleeding-related death as a competing event, according to the method of Fine and Gray (29). Results are reported as unadjusted and adjusted subhazard ratios (SHR) with corresponding 95% CIs and p-values. SHR are adjusted for the RIETE score (22,23) and periods of anticoagulation during follow-up as a time-varying covariate for both endpoints. The RIETE score was only adjusted for anticoagulation. Missing values in score items were assumed to be normal. All analyses were done using Stata 15 (Stata Corporation, College Station, Texas, USA).

Results

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Patients' baseline characteristics

Patients' demographic characteristics and median biomarker values upon admission are listed in Table 2. At inclusion, patients with clinical relevant bleeding during follow-up tended to be older, were more likely to display an altered mental status, to be diabetic, known for cerebrovascular events, and to have been immobilized during the last three months (Table 2). Of note, hs-cTnT as well as the RIETE score upon inclusion were significantly higher in patients that had a clinically relevant bleeding episode than those who did not during follow-up. There were no other significant differences between these two groups of patients (Table 2).

Table 2. Patients baseline characteristics

	All	**With CR Bleeding Event**	**Without CR Bleeding Event**	**p-value**
	% (n) or median (IQR)	% (n) or median (IQR)	% (n) or median (IQR)	
total N	230	64	166	
Age	75 (69-82)	77.0 (70.3-83.0)	74.0 (69.0-81.0)	0.050
Female gender	94 (41%)	25 (39%)	69 (42%)	0.729
DVT (all)	47 (20%)	12 (19%)	35 (21%)	0.694
Proximal DVT (versus distal)	41 (18%)	10 (16%)	31 (19%)	0.588
Systolic BP <100 mmHg	4 (2%)	0 (0%)	4 (2%)	0.210
Heart rate ≥110 beats/min	27 (12%)	4 (6%)	23 (14%)	0.108
Respiratory rate ≥30/min	9 (4%)	2 (3%)	7 (4%)	0.649
Oxygen saturation <90%	23 (10%)	3 (5%)	20 (12%)	0.062
Temperature <36°C	18 (8%)	4 (6%)	14 (8%)	0.577
Body mass index (kg/m^2)	26.6 (23.9-29.8)	26.6 (23.0-29.6)	26.6 (24.2-29.9)	0.609
Altered mental status	6 (3%)	4 (6%)	2 (1%)	0.031
Diabetes mellitus	35 (15%)	14 (22%)	21 (13%)	0.081
Coronary heart disease	41 (18%)	13 (20%)	28 (17%)	0.541
Heart failure†	23 (10%)	9 (14%)	14 (8%)	0.202
Arterial hypertension	150 (65%)	40 (63%)	110 (66%)	0.591
Chronic renal disease††	39 (17%)	12 (19%)	27 (16%)	0.653
Chronic lung disease¶	33 (14%)	11 (17%)	22 (13%)	0.446
Cerebrovascular disease‡	20 (9%)	9 (14%)	11 (7%)	0.073
Smoker (current or past)	116 (50%)	27 (42%)	89 (54%)	0.146
Current oestrogen therapy	5 (2%)	1 (2%)	4 (2%)	0.689

during the last 3 months				
Major surgery during the last 3 months	33 (14%)	10 (16%)	23 (14%)	0.732
Immobilization during the last 3 months§	52 (23%)	20 (31%)	32 (19%)	0.052
Prior VTE	70 (30%)	21 (33%)	49 (30%)	0.627
Prior DVT	42 (18%)	13 (20%)	29 (17%)	0.617
Active cancer#	39 (17%)	10 (16%)	29 (17%)	0.738
Concomitant antiplatelet therapy	63 (33%)	20 (37%)	43 (31%)	0.496
hs-cTnT (ng/l)	16.6 (8.2-33.9)	27.5 (12.5-47.2)	14.6 (6.8-28.7)	<0.001
hs -cTnT > 14 pg/ml	132 (57%)	46 (72%)	86 (52%)	0.006
NT-proBNP (pg/ml)	634.2 (227.2-2191.8)	957.0 (334.1-2286.3)	554.7 (186.4-2134.5)	0.187
NT-proBNP > 300 pg/ml	157 (68%)	49 (77%)	108 (65%)	0.093
PESI score	94.0 (80.0-110.3)	91.5 (79.3-114.0)	95.0 (80.0-109.0)	0.794
PESI > 85	150 (65%)	41 (64%)	109 (66%)	0.819
RIETE score	2.0 (2.0-3.5)	2.5 (2.0-3.9)	2.0 (1.0-3.5)	0.029
RIETE > 4	31 (13%)	13 (20%)	18 (11%)	0.059
Ratio RVEDD¶¶/LVEDD‡‡ > 0.9	60 (26%)	19 (30%)	41 (25%)	0.730

Data were missing for ratio RVEDD/LVEDD > 0.9 (20%), respiratory rate (17%), oxygen (7%), temperature (2%), estrogen therapy (0.4%), smoking status (0.4%), and BMI (0.4%).

†Acute heart failure NYHA class II/IV during the last 3 months, left or right heart failure, known left ventricular ejection fraction of <40%, known history of systolic or diastolic heart failure, or forward or backward heart failure.
††Chronic glomerulonephritis, cystic kidney disease, diabetic or hypertensive nephropathy, myeloma-related nephropathy, or chronic interstitial nephritis.
¶Chronic obstructive pulmonary disease, bronchiectasies, cystic fibrosis, lung fibrosis, or active asthma.
‡Transient ischemic attack or history of ischemic or hemorrhagic stroke.
§Fracture or cast of the lower extremity, voyage in sitting position for >6 hours during the last 3 months, or bed rest >72 hours.
#Cancer (solid or hematologic) requiring surgery, palliative care during the last 3 months, radiotherapy, or chemotherapy.
¶¶RVEDD: right ventricular end-diastolic diameter
‡‡LVEDD: left ventricular end-diastolic diameter

Abbreviations:
DVT: deep venous thrombosis

Incidence of endpoints according to different follow-up period

Clinically relevant bleeding was observed in 8.8% (20/230) of patients up to 1 month, 12.3% (28/230) up to 3 months and 29.1% (64/230) up to 24 months.

Major bleeding was seen in 6.2% (14/230) of patients up to 1 month, 7.0 % (16/230) up to 3 months and 14.1% (31/230) up to 24 months (Table S1 - supplementary data).

Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

Associations of cardiac biomarkers, PESI and RIETE score with study endpoints

As shown in Table 3 and Fig. 1, with the exception of the PESI score that showed no discrimination at any time during follow-up, both cardiac biomarkers and the RIETE score displayed a significant discriminative power for clinically relevant bleeding. hs-cTnT had the highest prognostic accuracy for the occurrence of clinically relevant bleeding at one month but was not statistically superior to the RIETE score (respective C-statistics: 0.77 vs 0.67, p=0.118). When hs-cTnT was added to the RIETE score, the C-statistics increased significantly from 0.67 (95% CI: 0.55-0.79) to 0.78 (95% CI: 0.67-0.82, p=0.023). On the other hand, adding the RIETE score to hs-cTnT did not substantially increase the C-statistics (0.77 to 0.78, p=0.782). Similar trends were observed with major bleeding (Table 4).

Table 3. C-statistics evolution and comparison for biomarkers, RIETE and PESI score for clinically relevant bleeding

	C-statistics* (95% CI)	p-value
1 month		
hs-cTnT (ng/l)	0.77 (0.66-0.88)	
NT-proBNP (pg/ml)	0.63 (0.52-0.74)	
PESI score	0.50 (0.36-0.64)	
RIETE score	0.67 (0.55-0.79)	
hs-cTnT (ng/l) added to RIETE score	0.78 (0.67-0.89)	0.023
RIETE score added to hs-cTnT (ng/l)	0.78 (0.67-0.89)	0.782
C-statistics comparison		
hs-cTnT (ng/l) vs NT-proBNP (pg/ml)		0.009
hs-cTNT (ng/ml) vs RIETE score		0.118
NT-proBNP (pg/ml) vs RIETE score		0.424
3 months		
hs-cTnT (ng/l)	0.75 (0.66-0.84)	
NT-proBNP (pg/ml)	0.63 (0.53-0.72)	
PESI score	0.51 (0.40-0.63)	
RIETE score	0.66 (0.55-0.76)	
hs-cTnT (ng/l) added to RIETE score	0.75 (0.65-0.84)	0.017

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RIETE score added to hs-cTnT (ng/l)	0.75 (0.65-0.84)	0.923
C-statistics comparison		
hs-cTnT (ng/l) vs NT-proBNP (pg/ml)		0.013
hs-cTNT (ng/ml) vs RIETE score		0.085
NT-proBNP (pg/ml) vs RIETE score		0.550
24 months		
hs-cTnT (ng/l)	0.67 (0.61-0.74)	
NT-proBNP (pg/ml)	0.58 (0.52-0.65)	
PESI score	0.53 (0.46-0.61)	
RIETE score	0.61 (0.54-0.68)	
hs-cTnT (ng/l) added to RIETE score	0.67 (0.60-0.74)	0.034
RIETE score added to hs-cTnT (ng/l)	0.67 (0.60-0.74)	0.667
C-statistics comparison		
hs-cTnT (ng/l) vs NT-proBNP (pg/ml)		0.005
hs-cTNT (ng/ml) vs RIETE score		0.104
NT-proBNP (pg/ml) vs RIETE score		0.510

*all variables are used continuous

Table 4. C-statistics evolution and comparison for biomarkers, RIETE and PESI score for major bleeding

	C-statistics* (95% CI)	p-value
1 month		
hs-cTnT (ng/l)	0.73 (0.59-0.88)	
NT-proBNP (pg/ml)	0.63 (0.51-0.76)	
PESI score	0.49 (0.35-0.64)	
RIETE score	0.68 (0.54-0.82)	
hs-cTnT (ng/l) added to RIETE score	0.74 (0.60-0.88)	0.069
RIETE score added to hs-cTnT (ng/l)	0.74 (0.60-0.88)	0.870
C-statistics comparison		
hs-cTnT (ng/l) vs NT-proBNP (pg/ml)		0.045
hs-cTNT (ng/ml) vs RIETE score		0.441
NT-proBNP (pg/ml) vs RIETE score		0.527
3 months		
hs-cTnT (ng/l)	0.75 (0.62-0.88)	
NT-proBNP (pg/ml)	0.67 (0.55-0.78)	
PESI score	0.55 (0.40-0.69)	
RIETE score	0.70 (0.57-0.83)	
hs-cTnT (ng/l) added to RIETE score	0.76 (0.63-0.88)	0.043
RIETE score added to hs-cTnT (ng/l)	0.76 (0.63-0.88)	0.925
C-statistics comparison		
hs-cTnT (ng/l) vs NT-proBNP (pg/ml)		0.054
hs-cTNT (ng/ml) vs RIETE score		0.418
NT-proBNP (pg/ml) vs RIETE score		0.578
24 months		
hs-cTnT (ng/l)	0.65 (0.54-0.75)	

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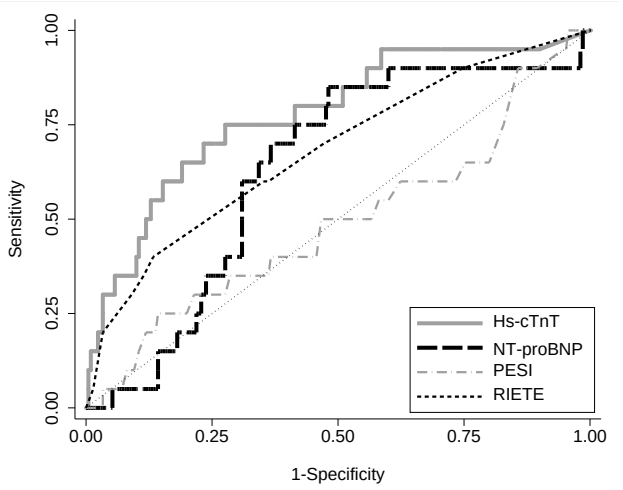
NT-proBNP (pg/ml)	0.62 (0.53-0.71)	
PESI score	0.53 (0.43-0.63)	
RIETE score	0.66 (0.56-0.76)	
hs-cTnT (ng/l) added to RIETE score	0.67 (0.57-0.77)	0.461
RIETE score added to hs-cTnT (ng/l)	0.67 (0.57-0.77)	0.555
C-statistics comparison		
hs-cTnT (ng/l) vs NT-proBNP (pg/ml)		0.497
hs-cTNT (ng/ml) vs RIETE score		0.840
NT-proBNP (pg/ml) vs RIETE score		0.457

*all variables are used continuous

On the other hand, the prognostic accuracy of NT-proBNP was substantially lower for the primary endpoint with C-statistics value of 0.63 (95% CI: 0.52 – 0.74), 0.63 (95% CI: 0.53 – 0.72) and 0.58 (95% CI: 0.52 – 0.65) at 1, 3, and 24 months, respectively. The PESI score did not predict the primary outcome with significant accuracy at any time of the follow-up (Table 3 and Fig. 1).

Fig 1. ROC curve analysis for clinically relevant bleeding at 1 month. ROC curves for hs-cTnT, NT-proBNP, RIETE and PESI score are shown.



Corroborating these results, competing-risks regression analyses indicated that values of hs-cTnT above 14 ng/l were significantly associated with clinically relevant bleeding at 24 months before (SHR 2.25, 95% CI: 1.32 – 3.86) and after (SHR 1.87, 95% CI: 1.05 – 3.34)

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adjustment for the RIETE score (Table 5). When used as a continuous variable, hs-cTnT was significantly associated with clinically relevant bleeding over the 24 months follow-up period after adjustment for RIETE score with SHR (95% CI) ranging from 1.58 (1.31 – 1.92) up to 1 month to l.31 (1.10 – 1.55) up to 24 months per log-unit increase. Regarding NT-proBNP values above 300 pg/ml, significant associations with the primary endpoint were observed up to 3 months (SHR: 4.09, 95% CI: 1.23 – 13.59) and 24 months (SHR: 1.77, 95% CI: 1.01 – 3.10) before adjustment. However, after adjustment, associations were not significant anymore. Unlike hs-cTnT, NT-proBNP was not significantly associated with clinically relevant bleeding at any time after adjustment for RIETE score when used as a continuous variable. PESI score was not associated with the primary endpoint at any time while RIETE score showed an increased SHR ranging between 1.58 (95% CI: 1.16 – 2.16) up to 1 month and 1.30 (95% CI: 1.07 – 1.57) up to 24 months (Table 5). Analysis results for major bleeding showed similar trends (Table S2 - supplementary data).

Table 5. Association of biomarkers, PESI and RIETE score with clinically relevant bleeding.

	Crude SHR (95% CI)	p-value	Adjusted SHR* (95% CI)	p-value
1 month				
hs-cTnT >14ng/l	4.43 (1.30 - 15.07)	0.017	3.16 (0.86 - 11.68)	0.084
hs-cTnT (ng/l)[1]	1.59 (1.31 - 1.93)	<0.001	1.58 (1.31 - 1.92)	<0.001
NT-proBNP >300pg/ml	4.30 (0.99 - 18.69)	0.052	3.00 (0.74 - 12.14)	0.124
NT-proBNP (pg/ml)[1]	1.23 (0.95 - 1.60)	0.120	1.06 (0.81 - 1.39)	0.676
PESI score[2]	0.99 (0.81 - 1.20)	0.900	0.83 (0.63 - 1.09)	0.182
RIETE score[3]	1.58 (1.16 - 2.16)	0.004	1.60 (1.17 - 2.19)	0.004
3 months				
hs-cTnT >14ng/l	3.70 (1.42 - 9.64)	0.008	2.68 (0.99 - 7.26)	0.053
hs-cTnT (ng/l)[1]	1.52 (1.26 - 1.83)	<0.001	1.51 (1.26 - 1.82)	<0.001
NT-proBNP >300pg/ml	4.09 (1.23 - 13.59)	0.021	2.95 (0.92 - 9.52)	0.070
NT-proBNP (pg/ml)[1]	1.26 (1.01 - 1.57)	0.043	1.10 (0.88 - 1.37)	0.386
PESI score[2]	1.02 (0.87 - 1.20)	0.781	0.88 (0.69 - 1.14)	0.335
RIETE score[3]	1.55 (1.19 - 2.03)	0.001	1.56 (1.20 - 2.04)	0.001
24 months				
hs-cTnT >14ng/l	2.25 (1.32 - 3.86)	0.003	1.87 (1.05 - 3.34)	0.034

Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

hs-cTnT (ng/l)[1]	1.34 (1.14 - 1.58)	<0.001	1.31 (1.10 - 1.55)	0.002
NT-proBNP >300pg/ml	1.77 (1.01 - 3.10)	0.046	1.40 (0.77 - 2.54)	0.266
NT-proBNP (pg/ml)[1]	1.10 (0.94 - 1.28)	0.228	1.01 (0.87 - 1.19)	0.864
PESI score[2]	1.03 (0.92 - 1.14)	0.638	0.95 (0.83 - 1.10)	0.486
RIETE score[3]	1.30 (1.07 - 1.57)	0.007	1.32 (1.09 - 1.60)	0.004

[1]Biomarkers were log-transformed and used continuous. Effects (SHRs) are expressed per one log-unit increase.
[2] Effects (SHRs) are expressed per 10 score points increase.
[3] Effects (SHRs) are expressed per score point increase.
*adjusted for RIETE score and periods of anticoagulation as a time-varying covariate. The RIETE score itself was only adjusted for anticoagulation.

Kaplan-Meier curves showed that patients with either hs-cTnT or NT-proBNP values above the pre-specified cut-off had a significantly higher cumulative incidence of clinically relevant bleeding up to 24 months than patients with values below the cut-off (37% vs 23% for NT-proBNP and 41% vs 20% for hs-cTnT, Fig. 2). Regarding major bleeding, only NT-proBNP values above the pre-specified cut-off had a significantly higher cumulative incidence of events compared to values below the cut-off (Fig. S3 - supplementary data).

Fig 2. Cumulative incidence of clinically relevant bleeding by level of hs-cTnT (left panel) and NT-proBNP (right panel). High versus low levels are based on pre-specified cut-offs (>14 ng/l for hs-cTnT and >300 pg/ml for NT-proBNP).

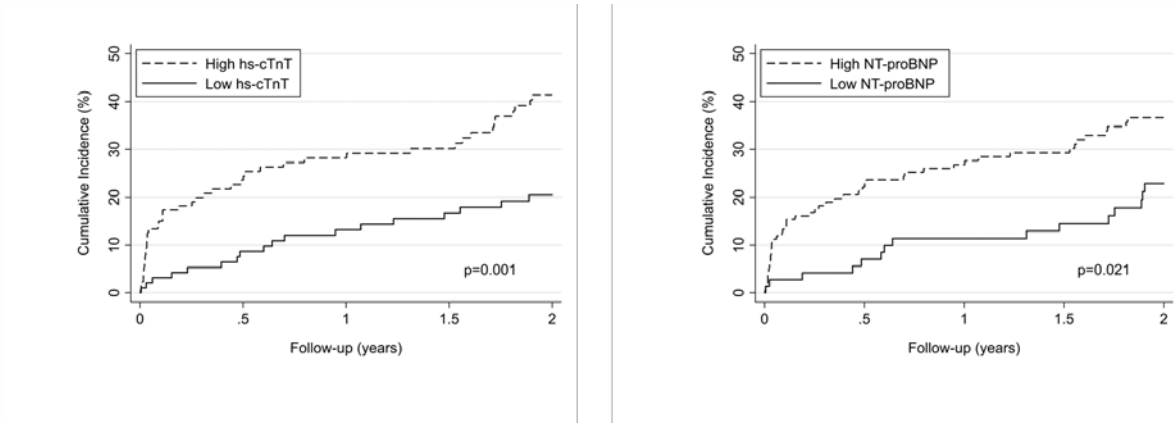

Table 6 summarizes specificity, sensitivity, and predictive values for each cardiac biomarker, PESI and RIETE score regarding clinically relevant bleeding over time. Both hs-cTnT and NT-proBNP tend to have a higher negative predictive value (NPV) than RIETE score at any time point considered. At the pre-specified cut-offs for NT-proBNP (300 pg/ml) and hs-cTnT

Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

(14 ng/L), NPVs were 97.3% (95% CI: 90.5 – 99.2) and 96.9% (95% CI: 91.4 – 99.0), respectively, up to 1 month and remained over 79.5% (95% CI: 68.8 – 87.1) and 81.6% (95% CI: 72.8 – 88.1), respectively, during the 24 months follow-up period. RIETE score showed slightly lower NPV values ranging between 93.5% (95% CI: 89.1 – 96.1) up to 1 month and 74.4% (95% CI: 67.9 – 79.9) up to 24 months. Values for major bleeding showed similar trends (Table S4 - supplementary data).

Table 6. Evolution of sensitivity, specificity, and predictive values over time with clinically relevant bleeding.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV[1] (95% CI)	NPV[2] (95% CI)
1 month				
hs-cTnT >14ng/l	85.0 (64.0-94.8)	45.2 (38.7-52.0)	12.9 (8.2-19.7)	96.9 (91.4-99.0)
NT-proBNP >300pg/ml	90.0 (69.9-97.2)	33.8 (27.8-40.4)	11.5 (7.4-17.4)	97.3 (90.5-99.2)
PESI score > 85	60.0 (38.7-78.1)	34.3 (28.2-40.9)	8.0 (4.6-13.5)	90.0 (81.5-94.8)
RIETE score > 4	35.0 (18.1-56.7)	88.6 (83.6-92.2)	22.6 (11.4-39.8)	93.5 (89.1-96.1)
3 months				
hs-cTnT >14ng/l	82.1 (64.4-92.1)	46.0 (39.3-52.9)	17.4 (11.9-24.8)	94.9 (88.6-97.8)
NT-proBNP >300pg/ml	89.3 (72.8-96.3)	34.7 (28.4-41.4)	15.9 (11.0-22.5)	95.9 (88.6-98.6)
PESI score > 85	60.7 (42.4-76.4)	34.2 (28.0-40.9)	11.3 (7.2-17.4)	86.3 (77.0-92.1)
RIETE score > 4	32.1 (17.9-50.7)	89.1 (84.1-92.7)	29.0 (16.1-46.6)	90.5 (85.6-93.8)
24 months				
hs-cTnT >14ng/l	71.9 (59.9-81.4)	48.2 (40.7-55.7)	34.8 (27.3-43.3)	81.6 (72.8-88.1)
NT-proBNP >300pg/ml	76.6 (64.9-85.3)	34.9 (28.1-42.5)	31.2 (24.5-38.8)	79.5 (68.8-87.1)
PESI score > 85	64.1 (51.8-74.7)	34.3 (27.5-41.8)	27.3 (20.8-35.0)	71.3 (60.5-80.0)
RIETE score > 4	20.3 (12.3-31.7)	89.2 (83.5-93.0)	41.9 (26.4-59.2)	74.4 (67.9-79.9)

[1]PPV: positive predictive value
[2]NPV: negative predictive value

Discussion

The major finding of this study is that, among both cardiac biomarkers, only hs-cTnT is found to be an independent predictor of clinically relevant bleeding susceptible to provide incremental discriminatory power when added to the RIETE score for bleeding risk prediction in patients anticoagulated for non-high risk PE. On the contrary, hs-cTnT C-statistics is not

Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

substantially modified after addition of the RIETE score. Even though C-statistics comparisons between cardiac biomarkers and RIETE score should be considered exploratory at the present time in PE, these hypothesis-generating results are very similar to what has been shown in the ARISTOTLE trial for hs-cTnT. Indeed, in this study testing the efficacy and safety of apixaban in preventing ischemic stroke in more than 14800 patients with atrial fibrillation (AF), hs-cTnT levels upon admission were found to be significant predictors of subsequent major bleeding. Moreover, hs-cTnT levels improved the C-statistics of the esthablished CHA2DS2VASc score (based on the following items: congestive heart failure, hypertension, 75 years of age and older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, 65 to 74 years of age, gender) from 0.591 to 0.629 ($p < 0.0001$) regarding the risk of major bleeding (30). Although NT-proBNP levels also improved risk stratification beyond the CHA2DS2VASc risk score, they did not predict subsequent major bleeding risk (31). If both NT-proBNP and hs-cTnT were shown to be appealing candidates for risk stratification in PE (6–12), the current results lend weight to the possibility that hs-cTnT could be the best to capture bleeding propensity upon anticoagulation. In addition, despite being non-significant, C-statistics differences observed between hs-cTnT and the RIETE score (Δ=0.10) is still of a magnitude order that could be perceived as substantial (32). Regarding major bleeding assessment, our results show the same trends with a few exceptions, notably at 24 months of follow-up where RIETE score C-statistics is found to be superior to hs-cTnT. On the other hand, RIETE score is found to be superior to NT-proBNP at any time. Of note, PESI score is not shown to be associated with endpoints in this study. This is not surprising since it has not been developed to predict hemorrhagic complications.

The pathophysiological reasons underlying bleeding risk prediction differences between hs-cTnT and NT-proBNP are still poorly understood and are most likely multifactorial. Indeed, aside myocardial necrosis and pressure overload, hs-cTn levels are known to be markedly

Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

influenced by age, myocardial apoptosis and fibrosis, and cardiomyocytes turn-over (33). Because cTn (mostly cTnI so far) have been shown to act as anti-angiogenic factors susceptible to disrupt endothelial integrity (18–21), we cannot exclude the fact that hs-cTnT elevations could also reflect the indivual bleeding propensity. Even without a complete understanding of the underlying mechanisms associating hs-cTnT with the hemorrhagic risk, hs-cTnT level below 14 ng/L shows an elevated (96.9%) negative predictive value (NPV) for a subsequent haemorragic event in PE and this test is available in most routine laboratories. Whether hs-cTnT could represent an attractive candidate to influence the selection of non-massive PE patients susceptible to benefit from a more aggressive treatment than standard anticoagulation alone remains an open question. Being at the opposite of most risk stratification concepts elaborated so far in non-massive PE, such hypothesis warrants further investigations, especially regarding the definition of an optimal cut-off to be used for such purpose.

Despite not being optimal for bleeding risk assessment in a rule-in strategy, hs-cTnT values below 14 ng/l show a higher NPV than RIETE score at any time for clinically relevant bleeding with value of 96.9% (95% CI: 91.4-99.0) versus 93.5% (95% CI: 89.1-96.1) at 1 month, respectively. In general, hs-cTnT and NT-proBNP NPVs are similar. In contrast, both hs-cTnT and NT-proBNP display, at the pre-specified cut-off values, positive predictive values that were not suitable, at least for the elderly, to identify patients with high risk for bleeding.

This study has several limitations. First, the number of events was limited. Although we observed significant associations with the primary endpoint when predictors were used continuous, these associations failed to reach significance when considered as dichotomous in adjusted analyses. Furthermore, the same trend was observed for the secondary endpoint indicating that some of the negative findings values reported here are likely to be ascribed to a

Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

power issue. Therefore, knowing whether the pre-specified cut-off for biomarkers used in acute coronary syndrome is adequate for bleeding risk stratification has to be answered.

Another limitation resides in the fact that we did not measure the Growth Differentiation Factor 15 (GDF-15), known to bare strong CV prognostic values in different clinical settings including PE (34,35), as well as to be a strong predictor of major bleeding in patient anticoagulated for AF (36). These findings led to the validation of a biomarker-based score entitled ABC (age, biomarkers, clinical history)-bleeding risk score in AF patients receiving oral anticoagulant therapy where GDF-15 was one of the most contributing factors (37). Therefore, the question whether GDF-15 would be more strongly associated with major bleeding risk in PE than hs-cTnT certainly remains of interest. Another important limitation of this study resides in the fact that that due to study design, we did not included PE patients requiring thrombolysis. Therefore, our results cannot be extrapolated to thrombolysed patients.

Due to a power issue associated with a low number of primary endpoint events in chronic kidney failure and cancer patients, such confounding factors cannot be excluded as well as the consequences of different anticoagulant therapy on the occurrence of bleeding.

Finally, the validity of the present results in PE patients that are younger than 65 years-old has to be established.

Conclusion

This hypothesis-generating study suggests that hs-cTnT has the highest discriminative accuracy among tested cardiac biomarkers and the RIETE score for predicting clinically relevant bleeding. Moreover, given their relatively high negative predictive values for hemorrhagic complications, knowing whether cardiac biomarkers assessment would improve

the risk/benefit ratio of thrombolysis in NMPE with radiological signs of right ventricular dysfunction remains to be demonstrated.

Author Contributions statement

Conceived and designed the experiments: DA MR HB MM EG NV. Performed the experiments: NV OG. Analyzed the data: AL NV. Wrote the paper: AS NV MM AL OG EG HB DA MR.

Funding and Conflict of interest statement

This cohort study was supported by the Swiss National Science Foundation (Grant no. 33CSO-122659/139470: http://p3.snf.ch/project-139470). Reagents costs were partly supported by Roche (Switzerland), and Thermo Scientific (BRAHMS AG, Hennigsdorf/Berlin, Germany) which were not involved in data analyses or results interpretation. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors have no other conflict of interest to disclose.

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Accepted author's manuscript. Published in final edited form as: Thrombosis Research. 2020; 185: 5-12. Publisher DOI: https://doi.org/10.1016/j.thromres.2019.11.006

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